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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/837,537	04/18/2001	Simon Lodewijk Scharpe	702-010673	7589

7590 07/28/2004

Barbara E. Johnson
WEBB ZIESENHEIM LOGSDON ORKIN & HANSON, P.C.
700 Koppers Building
436 Seventh Avenue
Pittsburgh, PA 15219-1818

EXAMINER	
RUSSEL, JEFFREY E	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/837,537	SCHARPE ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/623,752.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. On June 4, 2004, a supplemental amendment was received from Applicants which crossed in the mail with the Office action mailed June 2, 2004. Accordingly, this new non-final Office action is being issued. The shortened statutory period for response will be re-set based upon the mailing date of this Office action. However, the supplemental amendment does not affect any of the objections or rejections set forth in the Office action mailed June 2, 2004 and repeated below.

2. The Sequence Listing filed March 22, 2004 is approved.

3. The claim for priority inserted at page 1 of the specification, after the title, by the preliminary amendment filed April 18, 2004 and amended on June 2, 2004 is objected to because this application is a continuation-in-part, not a continuation, of parent application 09/623,752. This application contains subject matter not disclosed in parent application 09/623,752. In particular, this application discloses a definition of R1 and R2 in claim 1 where R1 and R2 can be (l), (m), (n), (o), or (p) regardless of the identity of X. In the original disclosure of parent application 09/623,752, R1 and R2 can be these possibilities only when X is AA-ala (see page 9, lines 18-26, and originally-filed claim 8). Because this application discloses subject matter not disclosed in the parent application, this application can only be a continuation-in-part, not a continuation, of the parent application.

Any amended benefit claim submitted by Applicants in response to the above objection will not be timely filed within the time period set forth in 37 CFR 1.78(a)(2) or (a)(5). If the application is an application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months

from the filing date of the prior application. If the application is a nonprovisional application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the reference to the prior application must be made during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, applicant must file a petition for an unintentionally delayed benefit claim under 37 CFR 1.78(a)(3) or (a)(6). The petition must be accompanied by: (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted); (2) a surcharge under 37 CFR 1.17(t); and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Note that the requirement to petition applies when the relationship between parent applications is incorrectly stated, as well as when a priority claim is completely missing from an application. See the Notice by Deputy Commissioner Kunin dated February 24, 2003, at http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/benefitclaims.pdf.

The status of parent application 09/623,752 needs to be updated in the priority claim inserted into the specification by the preliminary amendment filed April 18, 2001 and amended on June 4, 2004.

Correction is required.

4. A copy of an oath or declaration under 37 CFR 1.63 has not yet been scanned into the image file wrapper of this application. Assuming that Applicants submitted a copy of the oath or declaration filed in parent application 09/623,752, this copy of the oath or declaration is objected to because 37 CFR 1.63(e) requires that a newly executed oath or declaration be filed in any continuation-in-part application. See section 2 above as to why this application is a continuation-in-part, not a continuation, of parent application 09/623,752. Correction is required.

5. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The claim limitation in claim 1 that R1 and R2 can be (l), (m), (n), (o), or (p) regardless of the identity of X, is not recited in the instant specification.

6. The disclosure is objected to because of the following informalities: At page 14, line 6, "disinfectants" is misspelled. At page 15, line 11, "sclerosis" is misspelled. Appropriate correction is required.

7. Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-26 are indefinite because the general formulas recited in the claims and the claimed definitions of the X substituents are inconsistent with the specific claimed examples of compounds falling within the general formula. In particular, the general formulas and the claimed definitions of the X substituents imply that the phosphonate group is attached to the carbonyl group of an amino acid residue, whereas the specific claimed examples of compounds

falling within the general formula indicate that the phosphonate group replaces the carbonyl group of an amino acid residue. Accordingly, the structures of the compounds being claimed are unclear. Claims 1 is indefinite because at line 6 it states that the phenyl group is mono-, di-, or tri-substituted with R1 or R2. However, in general formula (I), only R_1 is shown as a possible substituent for the phenyl ring. Further, because R1 and R2 are always given the same definitions in the claims, it is not clear what the distinction is between an R1 substituent of the phenyl ring and an R2 substituent of the phenyl ring. There is no antecedent basis in the claim for the phrase "the phenyl group substituted with R1" at claim 1, line 8, because line 6 indicates that the phenyl group is substituted with R1 or R2, not just with R1. The "in particular..." phrases at claim 1, lines 14 and 17, are indefinite because it is not clear if the alkyl groups are to be limited to C_1-C_6 groups or not. It is suggested that the phrases could be deleted and made the subject matter of further dependent claims. At claim 1, page 58, line 8, "and" should be inserted before "sarcosine" so that standard Markush terminology is used. At claim 1, page 58, line 10, "and" should be inserted before "β-alanine" so that standard Markush terminology is used. At claim 2, line 5, the phrase "with in α position" is grammatically unclear, and is unclear as to whether the α-carbon or the α-amino group is being discussed. The relationship between the α position and the alkyl or aryl or aralkylmoiety is also unclear. At claim 3, line 21, "and" should be inserted before "β-alanine" so that standard Markush terminology is used. At claim 5, line 4, "and" should be inserted after the third comma so that standard Markush terminology is used. Claim 5, page 60, line 1, should be re-written as "protecting groups selected from the group consisting of..." so that standard Markush terminology is used. At claim 5, page 60, line 4, "and" should be inserted after the last comma in the line so that standard Markush terminology is

used. At claim 8, line 6, "and" should be inserted after the semicolon so that standard Markush terminology is used. It is not clear how claim 12, page 62, last line, should be interpreted with respect to those compounds which already specify hydrochloride or trihydrochloride salts, e.g., it is not clear if alternative salt forms for the compounds are embraced by the claim language. For analogous reasons, claim 15 is also indefinite. At claim 18, line 3, and claim 19, line 3, "and" should be inserted after the last comma in the line so that standard Markush terminology is used.

8. Claims 1-9, 11-13, and 16-26 are objected to because of the following informalities: In general formula (I) as recited in claim 1, "R_1" should be changed to "R1" so that the substituent name is consistent throughout the claims. At claim 1, line 23, and page 58, lines 7-8, "thioproline" is repeated. At claim 1, line 25, and claim 3, line 10, "naphthylglycine" is misspelled. At claim 1, page 58, line 1, and claim 3, line 14, a comma should be inserted after "penicillamine". At claim 1, page 58, line 6, the first beginning parenthesis in the line is unmatched. At claim 1, page 58, line 8, and claim 3, line 20, "carboxylacid" should be changed to "carboxylic acid". At claim 1, page 58, line 9, the semicolon after "acid" should be changed to a comma. At claim 1, page 58, line 16, "or" should be inserted after the fifth comma in the line. At claim 1, page 58, line 17, "or" should be inserted after the second comma in the line. At claim 2, line 6, "aralkyl moiety" should be two words. At claim 3, line 8, "tryptophan" is misspelled. At claim 3, lines 9 and 20-21, "thioproline" is repeated. At claim 8, lines 3 and 4, "or" should be inserted before the last group in each line. At claim 12, line 18, it is believed that the hyphen occurring after the beginning bracket should be deleted. At claim 17, line 2, the end parenthesis after "prolyl" is unmatched. At claim 22, line 2, and claim 24, line 2, "a

concentration of the compound of claim 35" should be re-written as "the compound of claim 35 in a concentration". Appropriate correction is required.

9. Claims 10-12,15, 18, and 19 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 10-12 do not further limit independent claim 1, upon which they ultimately depend, because independent claim 1 does not indicate that A can be a phenyl group. Claim 12 recites a compound at page 62, lines 25-26 which does not comprise any phenyl groups. Phenyl groups are required by the general formulas recited in claims 1 and 11, upon which claim 12 depends. To the extent that claim 15 embraces pharmaceutically acceptable salts, claim 15 is broader in scope than claim 14, upon which claim 15 depends, because claim 14 does not recite and therefore does not embrace pharmaceutically acceptable salts. Claims 12 (see especially lines 10-11, 14-15, and page 62, lines 11-12), 18, and 19 do not further limit the claims upon which they depend, because independent claim 1 does not permit R1 or R2 to be an N-protected amino acid, e.g., 4-(N-Bz-Gly-NH).

10. The effective filing date of instant claims 1-7, 9-11, 13, 16, 18-26 is deemed to be April 18, 2001, the filing date of the instant application. These claims are not deemed to be entitled under 35 U.S.C. 120 to the benefit of the filing date of parent application 09/623,752 because the parent application, under the test of 35 U.S.C. 112, first paragraph, does not disclose compounds in which R1 and R2 can be (l), (m), (n), (o), or (p) regardless of the identity of X. Accordingly, the WO Patent Application 99/46272, which published based upon Applicants' priority PCT application, is available as prior art against these claims under 35 U.S.C. 102(b).

The effective filing date of instant claims 8, 12, 14, 15, and 17 is deemed to be at least March 9, 1999, the filing date of parent PCT application PCT/EP99/01617. These claims are deemed to be entitled under 35 U.S.C. 120 and 365 to the benefit of the filing date of the parent PCT application because the parent PCT application, under 35 U.S.C. 112, first paragraph, discloses the claimed invention. Accordingly, the WO Patent Application 99/46272 is not available as prior art against these claims.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

12. Claims 1-7, 9-11, 13, 16, 18-26 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by the WO Patent Application 99/46272. See, e.g., the claims of the WO Patent Application '272. See Chester v. Miller, 15 USPQ2d 1333 (CAFC 1990) for a case in which claims which were not entitled to the benefit of the filing date of their priority applications were rejected over patents which issued based upon the priority applications.

13. Claims 1-7, 9, 11, 20, 22, 23, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 95/29691. The WO Patent Application '691 teaches DPP IV inhibitors (see page 2, line 18 - page 3, line 8) in which Z and Z^1 can be optionally substituted phenyl, X can be CH_2, and AA can be proline, phenylalanine, lysine, ornithine, H, or benzyloxycarbonyl. The inhibitors are used therapeutically in vitro and in vivo to inhibit serine proteases and to inhibit the process of organ transplant rejection. The inhibitors may be combined with carriers. See, e.g., page 4, lines 10-16; page 9, line 23 - page 10, line 2; and page 19, line 15 - page 20, line 3.

14. Claim 21 is rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 95/29691. Application of the WO Patent Application '691 is the same as in the above rejection of claims 1-7, 9, 11, 20, 22, 23, and 26. The WO Patent Application '691 does not teach combining its inhibitors with one or more additional therapeutic ingredients. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made

to combine the inhibitors of the WO Patent Application '691 with additional therapeutic ingredients because the purposes for which the inhibitors of the WO Patent Application '691 are to be used, e.g., AIDS treatment and prevention of tissue and organ transplant rejection, routinely involve the administration of multiple therapeutic agents, and combining the therapeutic agents in one pharmaceutical preparation would ease the invasiveness to the patient of their administration.

15. Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 95/29691 as applied against claims 1-7, 9, 11, 20, 22, 23, and 26 above, and further in view of the WO Patent Application 94/03055. The WO Patent Application '691 teaches the use of the inhibitors in preventing tissue and organ transplant rejection, but does not teach treating the tissue or organ to be transplanted with the inhibitor ex vivo. The WO Patent Application '055 teaches the use of DPP IV inhibitors to stimulate the growth of hematopoietic cells in vitro, which are then transplanted into another animal. See, e.g., page 2, line 36 - page 3, line 6. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the inhibitors of the WO Patent Application '691 to stimulate the growth of hematopoietic cells according to the method of the WO Patent Application '055, because the method of the WO Patent Application '055 is not limited to any particular DPP IV inhibitor, and because the WO Patent Application '691 discloses DPP IV inhibitors which are useful in the field of transplantation.

16. Claims 35-37, 40-45, 56, and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by the Lambeir et al article (Biochim. Biophys. Acta, Vol. 1290, pages 76-82). The Lambeir et

al article teaches in vitro DPP IV inhibitors including Pro-Pro-$(OPh)_2$, Pro-Ala-$(OPh)_2$ and Phe-Ala-$(OPh)_2$. See Table 1.

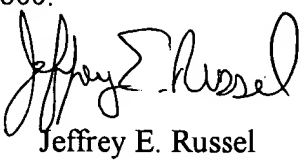
17. Claims 35-39, 45, 50, 56, and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by the Fastrez et al article (Tet. Lett., Vol. 30, pages 6861-6864). The Fastrez et al article teaches in vitro serine protease inhibitors including compounds 4c, 4d, 11b, 11c, 12b, and 12c. See Schemes 1 and 2.

18. On May 27, 2004, Applicants faxed a courtesy copy of the listing of references previously submitted in this application, because the previously-submitted listing of references was not available to the examiner in the image file wrapper system. However, this listing of references does not include all of the references cited during prosecution of the parent application; copies of all of the references cited in the listing of references are not present in the image file wrapper (note the ones crossed off in the copy of the listing of references attached to this Office action); citations in the listing of references are incomplete, missing complete titles of the publications and/or dates of publications and/or volume numbers (see, e.g., References BN-BQ, BS-BV, BX, CQ, and CS); and none of the references which are present in the image file wrapper are cited in the listing of references faxed to the examiner. To ensure that all references which Applicants intend to have considered and cited are officially made of record, it will be necessary for Applicants to submit a new IDS containing a revised listing of references with corrected and complete citations and containing copies of all references not already initialed on the attached copy of the listing of the references. With respect to the references which are currently present in the image file wrapper and which are not included in the listing of the references faxed to the examiner, it may be that these references were submitted in some other

application but were incorrectly scanned and indexed into this application. If this is so, the examiner can have these references removed from the image file wrapper for this application, but first he needs to have a complete listing of references to be cited so that he can determine whether the references should be removed or not.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Bruce Campell can be reached at (571) 272-0974. The fax number for formal communications to be entered into the record is (703) 872-9306; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

July 19, 2004